REMARKS

Claims 2-3, 6, and 9-10 have been cancelled, without prejudice.

Claim 1 has been amended to recite "[a] process for producing zeaxanthin and ß-cryptoxanthin which comprises cultivating a recombinant *Xanthophyllomyces dendrorhous* (*Phaffia rhodozyma*) ATCC96815 which expresses a ß-carotene hydroxylase gene that is originated from *Flavobacterium* sp. R1534 WT (ATCC21588) or *Erwinia herbicola* ATCC39368 in an aqueous nutrient medium under aerobic conditions, and isolating the resulting carotenoids from the cells of said recombinant microorganism or from the cultured broth, wherein the ß-carotene hydroxylase gene is expressed in the recombinant *Xanthophyllomyces dendrorhous* using an expression vector containing control sequences of glyceraldehyde-3-dehydrogenase gene." Support for these amendments is found in the specification at, for example, page 3, line 23 to page 4, line 4; in Examples 3 and 4; and in original claims 1, 2, 3, and 6. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l) (8th ed. Rev. 6, Sept. 2007, pp. 600-92 and 600-84).

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

Indefiniteness Rejection

Claim 6 was rejected under 35 USC § 112, second paragraph, for lack of antecedent basis. (Paper No. 20070726 at 2.) In making the rejection, the Examiner asserted that "[a]lthough claim 6 was amended to further limit 'the control sequences,' there is no reference to 'control sequences' earlier in claim 6 or in claim 1," and

"[t]herefore the examiner maintains that there is no antecedent basis for 'the control sequences' in claim 6." (*Id.* at 3.)

With a view toward furthering prosecution, claim 6 has been cancelled, without prejudice. Accordingly, the rejection of claim 6 has been rendered moot and should be withdrawn.

Written Description Rejection

Claim 3 was rejected under 35 USC § 112, first paragraph, as containing subject matter that was not described in the specification in such a way to convey that the inventors, at the time the application was filed, had possession of the claimed invention. (Paper No. 20070726 at 7.)

In making the rejection of claim 3, the Examiner asserted that "[c]laim 3 is broadly drawn, such that it applies to a genus of DNA sequences that are 'substantially homologous ... more than 90% identical amino acids' to a β-carotene hydroxylase gene of Flavobacterium sp R1534 WT." (*Id.* at 8.) The Examiner further asserted that "[w]hile the specification (page 3) teaches that the DNA sequences could share a preferable homology of more than 90% similarity to the β-carotene hydroxylase gene and exhibits the same enzymatic activity as the β-carotene hydroxylase gene from *Flavobacterium* R1534 (ATCC21588), the specification fails to detail the necessary structure of the substantially homologous DNA sequences." (*Id.*)

The Examiner then concluded that "a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed genus of DNA sequences that are 'substantially homologous'

to a β-carotene hydroxylase gene originated from *Flavobacterium* R1534 (ATCC21588)." (*Id.* at 10.)

With a view toward furthering prosecution, claim 3 has been cancelled, without prejudice. Accordingly, the rejection of claim 3 has been rendered moot and should be withdrawn.

Rejections under 35 USC § 103

Claims 1-3, 6, and 8 were rejected under 35 USC § 103(a) as being unpatentable over Brzostowicz *et al.*, U.S. Patent No. 6,969,595 ("Brzostowicz") in view of Van Ooyen, U.S. Patent No. 5,840,528 ("Van Ooyen 1"). (Paper No. 20070726 at 4 and Paper No. 20070202 at 7.)

For the reasons set forth below the rejection, respectfully is traversed.

Brzostowicz discloses "the production of carotenoid compounds from microorganisms which metabolize single carbon substrates as a sole carbon source." Col. 1, lines 12-15. Brzostowicz discloses that the "present invention provides for the expression of genes involved in the biosynthesis of carotenoid compounds in microorganisms which are able to use single carbon substrates as a sole energy source. Such microorganisms are referred to herein as C1 metabolizers. The host microorganism may be any C1 metabolizer which has the ability to synthesize isopentenyl pyrophosphate (IPP) the precursor for many of the carotenoids." Col. 14, lines 53-60. In addition, Brzostowicz discloses that:

> Accordingly the present invention provides a method for the production of a carotenoid compound comprising providing a transformed C1 metabolizing host cell which
>
> (a) grows on a C1 carbon substrate selected from the group consisting of methane and methanol; and

(b) comprises a functional Embden-Meyerhof carbon pathway, said pathway comprising a gene encoding a pyrophosphate dependent phosphofructokinase enzyme. Col. 17, lines 35-43.

Brzostowicz discloses that preferred C1 metabolizing host cells are methylotrophic bacteria, including "*Methylophilus*, *Methylobacillus*, *Methylobacterium*, *Hyphomicrobium*, *Xanthobacter*, *Bacillus*, *Paracoccus*, *Nocardia*, *Arthrobacter*, *Rhodopseudomonas*, and *Pseudomonas*." Col. 15, lines 16-30. In addition, Brzostowicz notes that the "ability to utilize single carbon substrates is not limited to bacteria but extends also to yeasts and fungi. ... Specific methylotrophic yeasts useful in the present invention include but are not limited to *Candida*, *Hansenula*, *Pichia*, *Torulopsis*, and *Rhodotorula*." Col. 15, lines 31-37.

Brzostowicz also discloses that "[n]ucleic acid fragments encoding a variety of enzymes implicated in the carotenoid biosynthetic pathway have been cloned into microorganisms which use single carbon substrates as a sole carbon source for the production of carotenoid compounds." Col. 7, lines 5-9. Specifically, Brzostowicz discloses that the nucleic acid fragment encodes "an enzyme in the carotenoid biosynthetic pathway." Col. 4, lines 39-41. Among the genes disclosed is the crtZ gene of *Flavobacterium* ATCC21588. Col. 25, line 36.

Brzostowicz further discloses a "method that produces higher yields of carotenoids from an inexpensive feedstock" to improve on the prior methods of producing carotenoids, which "suffer from low yields and reliance on expensive feedstocks." Col. 2, lines 48-52. Among such apparently unacceptable prior methods, Brzostowicz identifies a method of producing "Astaxanthin ... from *E. coli* and *Pfaffia rhodozyma*." Col. 2, lines 27-30.

Van Ooyen 1 discloses "transformed *Phaffia* strains, preferably transformed *Phaffia rhodozyma* strains ... [and] methods for transforming *Phaffia rhodozyma*." Col. 2, lines 14-17. Van Ooyen 1 also discloses "methods for obtaining expression of desired genes in *Phaffia*. ... Through cloning and expression of genes involved in the carotenoid biosynthetic pathway it also becomes possible to use *Phaffia rhodozyma* for obtaining desired carotenoids." Col. 2, lines 42-51. Van Ooyen 1 discloses that "[t]ransformation of *Phaffia rhodozyma* was performed in the following manner. *Phaffia* protoplasts were made using standard procedures and they were subsequently transformed with the transformation vector. Finally, the transformed *Phaffia* protoplasts were regenerated and selected on an appropriate selective medium." Col. 5, lines 12-17. Van Ooyen 1 "discloses for the first time a vector capable of transforming a *Phaffia* with concurrent expression of the cloned gene [and that the] vector contains the actin promoter and a marker gene." Col. 5, lines 25-34.

In making the rejection, the Examiner asserted that Brzostowicz discloses "'a method for the production of a carotenoid compound comprising ... [transforming] ... at least one isolated nucleic acid molecule encoding an enzyme in the carotenoid biosynthetic pathway under the control of suitable regulatory sequences ... under suitable growth conditions ... whereby an carotenoid compound is produced.' (col. 125, lines 44-57)." (Paper No. 20070202 at 8.) (Emphasis original.) The Examiner also asserted that Brzostowicz discloses that "'the isolated nucleic acid molecule encodes ... β-carotene hydroxylase' (col. 126, lines 53-57) ... [and that] 'the carotenoid compound is ... β-cryptoxanthin, ... zeaxanthin' (col. 127, line 39 - col. 128, line 5). " (*Id.*) The Examiner further asserted that Brzostowicz discloses that "the β-carotene hydroxylase

gene is originated from *Flavobacterium* sp. ATCC21588 (col. 25, line 36) ... [and] a method for producing zeaxanthin and β-cryptoxanthin, wherein the pH is 'maintained constant at 6.95' (col. 57, line 18) and incubation times of 0-69.5 hours (table 15; col. 58, lines 35-45) and at an incubation temperature of 30°C." (*Id.*)

The Examiner acknowledged, however, that Brzostowicz differs from the claimed invention in that Brzostowicz does not disclose "the use of genus *Xanthophyllomyces (Phaffia)* as the recombinant microorganism use[d] to express the recombinant proteins." (*Id.*)

To fill the acknowledged gap, the Examiner relied upon Van Ooyen 1 as disclosing "transformed *Phaffia rhodozyma* capable of producing carotenoids, including zeaxanthin (col. 2, line 50) through introduction of [a] plasmid comprising a suitable gene, 'crtZ' (col. 5, line 62-63) into *Phaffia rhodozyma*." (*Id.*) The Examiner asserted that Van Ooyen 1 discloses that the "transformed *Phaffia* 'is cultivated under conditions ... the range of 15°- 26°C. The preferred range is 20°-22°C.' (col. 6, line 24)." (*Id.* at 9.) The Examiner also asserted that Van Ooyen 1 discloses that "'[i]t is possible to produce other carotenoid precursors in the same way, in general all carotenoids that can be enzymatically derived from precursors of astaxanthin in *Phaffia* can be obtained.' (col. 6, lines 16-19)." (*Id.*)

The Examiner then concluded that "it would have been obvious ... to produce zeaxanthin and β-cryptoxanthin from recombinant *Phaffia* that expresses a β-carotenoid hydroxylase gene." (*Id.*) The Examiner contended that one "would have been motivated to make those modifications because *Phaffia rhodozyma* is a functionally equivalent microorganism that is useful for production of carotenoids." (*Id.*)

In Response to Applicants' arguments filed May 14, 2007, the Examiner, citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), asserted that "th[e] necessity for a 'reason or suggestion' is no longer required." (Paper No. 20070726 at 4.) Based solely on this interpretation of *KSR*, the Examiner then concluded that "[i]t would have been obvious to the person of ordinary skill in the art at the time of the invention ... to substitute a known equivalent element for another to obtain predictable results," and that "it would have been obvious to substitute *Phafia rhodozyma* as a functionally equivalent microorganism that is useful for production of carotenoids, for any of the microorganisms taught by Brzostowicz et al." (*Id.* at 4-5).

Initially, we note that claims 2-3 and 6 have been cancelled, without prejudice. Therefore, the rejection is moot and should be withdrawn with respect to claims 2-3 and 6.

With a view toward furthering prosecution, claim 1 has been amended to recite "[a] process for producing zeaxanthin and ß-cryptoxanthin which comprises cultivating a recombinant *Xanthophyllomyces dendrorhous* (*Phaffia rhodozyma*) ATCC96815 which expresses a ß-carotene hydroxylase gene that is originated from *Flavobacterium* sp. R1534 WT (ATCC21588) or *Erwinia herbicola* ATCC39368 in an aqueous nutrient medium under aerobic conditions, and isolating the resulting carotenoids from the cells of said recombinant microorganism or from the cultured broth, wherein the ß-carotene hydroxylase gene is expressed in the recombinant *Xanthophyllomyces dendrorhous* using an expression vector containing control sequences of glyceraldehyde-3-dehydrogenase gene."

It is well settled the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731-32 (2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence <u>of record</u>***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added). *See also Examination Guidelines for Determining Obviousness*, 72 Fed. Reg. 57526, 57528 (October 10, 2007) ("The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.").

Respectfully, we submit that the rejection is devoid of *any* evidence - or even argument - in support of the proposed combination. All that is there is the ***erroneous*** assertion that "th[e] necessity for a 'reason or suggestion' is no longer

required" in view of *KSR* and that "it would have been obvious to substitute *Phafia rhodozyma* as a functionally equivalent microorganism that is useful for production of carotenoids, for any of the microorganisms taught by Brzostowicz et al." (Paper No. 20070726 at 4.) The Supreme Court in *KSR* did not eliminate "th[e] necessity for a 'reason or suggestion' ..." as asserted by the Examiner. In fact, the Supreme Court in *KSR* stated that the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness. *KSR*, 127 S.Ct. at 1731-32. *See also Ex parte Noelle*, 2008 WL 55123, *4 (BPAI Jan. 3, 2008) (citing *KSR*) ("In making an obviousness determination over a combination of prior art references, it is important to ***identify a reason why*** persons of ordinary skill in the art would have attempted to make the claimed subject matter." The Board further observed in reversing a §103 rejection that "[t]he Examiner provides ***no evidence or articulated reasoning as to why*** one of ordinary skill in the art would purify isolated CD4+ T-cells in view of the ex vivo example using bone marrow in [the reference].") (emphasis added).

Indeed, the recent *Examination Guidelines for Determining Obviousness* promulgated in view of *KSR* explicitly state that "[t]he key to supporting any rejection under 35 U.S.C. 103 is ***the clear articulation of the reason(s) why*** the claimed invention would have been obvious." *Examination Guidelines for Determining Obviousness*, 72 Fed. Reg. 57526, 57528 (October 10, 2007) (emphasis added).

Here, what the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Brzostowicz using Van Ooyen 1 to arrive at the claimed method. As is well settled, an Examiner cannot

establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. June 28, 2007) (citing *KSR*) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). But this is precisely what the Examiner has done here. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

We further note that the rejection is legally deficient because it attempts to modify Brzostowicz in a manner inconsistent with its plain language. For example, Brzostowicz discloses "the expression of genes involved in the biosynthesis of carotenoid compounds in microorganisms which are able to use single carbon substrates as a sole energy source." Col. 14, lines 57-60. Brzostowicz discloses host cells which are microorganisms able to use single carbon substrates as a sole energy source, preferably bacteria. Col. 15, lines 16-30. To the extent that Brzostowicz discloses any yeast strains, they are "methylotrophic yeasts ... includ[ing] ... *Candida*, *Hansenula*, *Pichia*, *Torulopsis*, and *Rhodotorula*." Col. 15, lines 31-37. Brzostowicz's stated goal is to provide a "method that produces higher yields of carotenoids from an inexpensive feedstock" to improve upon the prior methods of producing carotenoids, which "suffer from low yields and reliance on expensive feedstocks." Col. 2, lines 48-

52. And, consistent with these goals, ***Brzostowicz clearly criticizes a method used to produce a carotenoid using "Pfaffia rhodozyma***." Col. 2, lines 27-30.

Thus, to modify Brzostowicz to utilize *Phaffia* requires one of skill in the art to disregard the specific disclosure in ***Brzostowicz that its method improves upon the use of Phaffia in the production of carotenoids***. We respectfully submit that Brzostowicz's criticism of the use of *Phaffia* ***cannot*** be ignored. And, indeed is a clear teach away from the present claims. Furthermore, the rejection points to no evidence or reasoning why one would ***ignore*** the explicit disclosure in *Brzostowicz* that using *Phaffia* to produce certain carotenoids suffers from a number of drawbacks. At best, such a disclosure would lead one skilled in the art to look to the identified methylotrophic yeasts disclosed or other similar strains – not to *Phaffia* – if there was some desire to modify the disclosed process.

At worst (for the Examiner), *Brzostowicz* is strong evidence in favor of the patentability of the present claims. Indeed, here, the claims recite exactly what *Brzostowicz* criticizes, namely using *Phaffia rhodozyma* in a process for producing zeaxanthin and ß-cryptoxanthin. As is well settled, doing what an asserted document teaches against is the antithesis of obviousness. *See, e.g., In re Buehler*, 515 F.2d 1134 (CCPA 1975) and *In re Rosenberger*, 386 F.2d 1015 (CCPA 1967). Thus, for this reason also, the rejection should be withdrawn.

Notwithstanding the legal infirmities noted above, assuming arguendo that Brzostowicz and Van Ooyen 1 are properly combinable, which they are not, the resulting combination fails to disclose or suggest claim 1 as amended. Accordingly, for

this additional reason, the rejection again fails to present a prima facie case for obviousness and should be withdrawn.

Claims 1-3, 6, and 8 were rejected under 35 USC § 103(a) as being unpatentable over Van Ooyen, WO1994/06918 ("Van Ooyen 2") in view of Cunningham, Jr. *et al.*, U.S. Patent No. 5,744,341 ("Cunningham"). (Paper No. 20070726 at 5-7 and Paper No. 20070202 at 10.)

For the reasons set forth below the rejection, respectfully is traversed.

Van Ooyen 2 discloses "transformed *Phaffia* strains, preferably transformed *Phaffia rhodozyma* strains ... [and] methods for transforming *Phaffia rhodozyma*." Page 3, lines 7-10. Van Ooyen 2 also discloses "methods for obtaining expression of desired genes in *Phaffia*. ... Through cloning and expression of genes involved in the carotenoid biosynthetic pathway it also becomes possible to use *Phaffia rhodozyma* for obtaining desired carotenoids." Page 3, line 34 - page 4, line 3. Van Ooyen 2 discloses that "[t]ransformation of *Phaffia rhodozyma* was performed in the following manner. *Phaffia* protoplasts were made using standard procedures and they were subsequently transformed with the transformation vector. Finally, the transformed *Phaffia* protoplasts were regenerated and selected on an appropriate selective medium." Page 8, lines 24-29. Van Ooyen 2 asserts that it "discloses for the first time a vector capable of transforming a *Phaffia* with concurrent expression of the cloned gene [and that the] vector contains the actin promoter and a marker gene." Page 9, lines 1-4.

Cunningham discloses "the DNA sequence for eukaryotic genes encoding ε [cyclase], isopentenyl pyrophosphate isomerase (IPP) and β-carotene hydroxylase as

well as vectors containing the same and hosts transformed with said vectors. ... [and] a method for augmenting the accumulation of carotenoids and production of novel and rare carotenoids." Col. 1, lines 8-14. Specifically, Cunningham discloses that it is an "object of this invention is to provide isolated eukaryotic genes which encode enzymes involved in carotenoid biosynthesis; in particular, ε cyclase, IPP isomerase and β-carotene hydroxylase." Col. 2, lines 34-37. Cunningham further discloses that the "DNA sequence encoding the β-carotene hydroxylase [was] isolated from *A. thaliana*." Col. 3, lines 35-37; Figure 5 (SEQ ID NO: 3).

In making the rejection, the Examiner asserted that Van Ooyen 2 discloses "Phaffia for carotenoid production (page 1, line 22 - page 2, line 29), and suggests that transformation of Phaffia with the crtZ gene can be used for the increased production of carotenoids, e.g. zeaxanthin (page 9, line 36 to page 10, line 6)." (Paper No. 20070202 at 10.) The Examiner also asserted that Van Ooyen 2 discloses "the conditions for cultivation of the latter microorganism ... (page 10, lines 30-36; page 11, lines 1-2; pages 12-17; page 21, lines 7-8)." (*Id.*)

The Examiner acknowledged, however, that Van Ooyen 2 differs from the claimed invention in that Van Ooyen 2 does not disclose the "production of β-cryptoxanthin in Phaffia." (*Id.*) To fill the acknowledged gap, the Examiner relied upon Cunningham as disclosing "the production of zeaxanthin and β-cryptoxanthin by a microorganism that produces carotenoids and that was transformed with the β-carotenoid hydroxylase gene from A. thaliana (col. 5, lines 35-39; col. 6, lines 37-45)." (*Id.* at 11.)

The Examiner then concluded that "it would have been obvious ... to produce zeaxanthin and β-cryptoxanthin in Phaffia." (*Id.*) The Examiner asserted that one "would have been motivated to make that modification because, '[t]hrough cloning and expression of genes involved in the carotenoid biosynthetic pathway it also becomes possible to use *Phaffia rhodozyma* for obtaining desired carotenoids. Desired carotenoid production includes increased production of ... carotenoids such as zeaxanthin,' (Van Ooyen, page 4, lines 1-6) and Cunningham et al. seek [a] 'method for augmenting the accumulation of carotenoids and production of novel and rare carotenoids. The present invention provides methods for controlling the ratio of various carotenoids in a host.' (Cunningham et al., col. 1, lines 11-15)." (*Id.*)

In Response to Applicants' arguments filed May 14, 2007, the Examiner, citing *KSR*, asserted that "th[e] necessity for a 'reason or suggestion' is no longer required." (Paper No. 20070726 at 6.) Based solely on this interpretation of *KSR*, the Examiner then concluded that "[i]t would have been obvious to the person of ordinary skill in the art at the time of the invention ... to substitute a known equivalent element for another to obtain predictable results," and that "it would have been obvious to substitute any equivalent β-carotene hydroxylase gene, including that of Erwinia herbicola to produce zeaxanthin and β-cryptoxanthin in Phaffia." (*Id.* at 6-7).

Initially, we note that claims 2-3 and 6 have been cancelled, without prejudice. Therefore, the rejection is moot and should be withdrawn with respect to claims 2-3 and 6.

With a view toward furthering prosecution, claim 1 has been amended to recite "[a] process for producing zeaxanthin and ß-cryptoxanthin which comprises

cultivating a recombinant *Xanthophyllomyces dendrorhous* (*Phaffia rhodozyma*) ATCC96815 which expresses a ß-carotene hydroxylase gene that is originated from *Flavobacterium* sp. R1534 WT (ATCC21588) or *Erwinia herbicola* ATCC39368 in an aqueous nutrient medium under aerobic conditions, and isolating the resulting carotenoids from the cells of said recombinant microorganism or from the cultured broth, wherein the ß-carotene hydroxylase gene is expressed in the recombinant *Xanthophyllomyces dendrorhous* using an expression vector containing control sequences of glyceraldehyde-3-dehydrogenase gene."

As noted above, when patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR*, 127 S.Ct. at 1731-32 (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley*, 60 USPQ2d at 1008. Moreover, the factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence of record***." *Lee*, 61 USPQ2d at 1433 (emphasis added). *See also Examination Guidelines for Determining Obviousness*, 72 Fed. Reg. 57526, 57528 (October 10, 2007) ("The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.").

Respectfully, we submit that the rejection is also devoid of *any* evidence - or even argument - in support of the proposed combination. Just as in the previous rejection, all that is there is the ***erroneous*** assertion that "th[e] necessity for a 'reason or suggestion' is no longer required" in view of *KSR* and that "it would have been obvious to substitute any equivalent β-carotene hydroxylase gene, including that of Erwinia herbicola to produce zeaxanthin and β-cryptoxanthin in Phaffia." (Paper No. 20070726 at 6-7.) The Supreme Court in *KSR* did not eliminate "th[e] necessity for a 'reason or suggestion' ..." as asserted by the Examiner. In fact, the Supreme Court in *KSR* stated that the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness. *KSR*, 127 S.Ct. at 1731-32. *See also Ex parte Noelle*, 2008 WL 55123, *4 (BPAI Jan. 3, 2008) (citing *KSR*) ("In making an obviousness determination over a combination of prior art references, it is important to ***identify a reason why*** persons of ordinary skill in the art would have attempted to make the claimed subject matter." The Board further observed in reversing a §103 rejection that "[t]he Examiner provides ***no evidence or articulated reasoning as to why*** one of ordinary skill in the art would purify isolated CD4+ T-cells in view of the ex vivo example using bone marrow in [the reference].") (emphasis added).

Indeed, the recent *Examination Guidelines for Determining Obviousness* promulgated in view of *KSR* explicitly state that "[t]he key to supporting any rejection under 35 U.S.C. 103 is ***the clear articulation of the reason(s) why*** the claimed invention would have been obvious." *Examination Guidelines for Determining Obviousness*, 72 Fed. Reg. 57526, 57528 (October 10, 2007) (emphasis added).

Here, what the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Van Ooyen 2 using Cunningham to arrive at the claimed method. As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem.*, 492 F.3d at 1357 (citing *KSR*) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Levengood*, 28 USPQ2d at 1301-02. But this is precisely what the Examiner has done here. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

The rejection also fails to point out where in either of Van Ooyen 2 or Cunningham a β-carotene hydroxylase gene from "*Flavobacterium* sp. R1534 WT (ATCC21588)" or "*Erwinia herbicola* ATCC39368" is disclosed or suggested. In fact, both Van Ooyen 2 and Cunningham do not disclose or suggest a β-carotene hydroxylase gene from any of these organisms. Accordingly, the rejection fails to demonstrate where in the cited documents each and every limitation of the currently claimed invention is disclosed or suggested. For this reason also, the rejection is fatally infirm and should be withdrawn.

Moreover, Van Ooyen 2 discloses "transformed *Phaffia* strains, preferably transformed *Phaffia rhodozyma* strains ... [and] methods for transforming *Phaffia*

rhodozyma." Col. 2, lines 14-17. Van Ooyen 2 does not disclose the transformation of any microorganism other than *Phaffia*, a eukaryotic organism.

Cunningham, on the other hand, discloses "the DNA sequence for ***eukaryotic genes*** encoding ε [cyclase], isopentenyl pyrophosphate isomerase (IPP) and β-carotene hydroxylase as well as vectors containing the same and hosts transformed with said vectors." Col. 1, lines 8-11. Cunningham discloses that the "method of the present invention comprises ***transforming a prokaryotic host with a DNA which may contain a eukaryotic or prokaryotic carotenoid biosynthetic gene***....." Col. 6, lines 65-67. Cunningham discloses that it is an "object of this invention is to provide isolated ***eukaryotic genes*** which encode enzymes involved in carotenoid biosynthesis; in particular, ε cyclase, IPP isomerase and β-carotene hydroxylase," specifically from *A. thaliana*. Col. 2, lines 34-37; col. 3, lines 35-37; Figure 5 (SEQ ID NO: 3). Cunningham does not disclose the transformation of any eukaryotic host with any prokaryotic gene, as claimed.

Van Ooyen 2 discloses the transformation of a eukaryotic organism (*Phaffia*) with prokaryotic genes. Cunningham, conversely discloses the transformation of prokaryotic organisms with eukaryotic (or prokaryotic) genes and specifically discloses the eukaryotic β-carotene hydroxylase gene from *A. thaliana*.

Again, there is simply no disclosure or suggestion in the cited documents, or any rationale, to combine Van Ooyen 2 and Cunningham in the manner suggested by the Examiner, to arrive at the claimed invention. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that ***the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is***

rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.") (emphasis added). Indeed, given the Examiner's conclusion that the art is "unpredictable" (see Paper No. 20070726 at 9), a disclosure or suggestion or even scientifically valid reasoning is required to combine Van Ooyen 2 and Cunningham, which are directed to transforming different systems (eukaryotic vs. prokaryotic). Accordingly, for this reason also, the rejection fails to present a *prima facie* case for obviousness and should be withdrawn.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). Even if properly combinable, which is not conceded, Van Ooyen 2 and Cunningham either alone or in combination fall far short of disclosing or suggesting what is currently claimed.

At best, in combination Van Ooyen 2 modified with Cunningham, as suggested by the Examiner, would produce a *Phaffia* transformed with a β-carotene hydroxylase gene from *A. thaliana*. But, that is ***not*** what is currently claimed. For this additional reason, the rejection is factually insufficient to support a rejection under 35 USC § 103 and should be withdrawn.

Claims 1-3, 6, and 8-10 were also rejected under 35 USC § 103(a) as being unpatentable over Brzostowicz in view of Van Ooyen 1 and further in view of Cunningham.[1] (Paper No. 20070726 at 11.)

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[1] We note that the rejection stated on p. 11 is based only on Brzostowicz in view of Van Ooyen 1. The rejection, however, appears to also rely on Cunningham. Accordingly, we have interpreted the rejection as based on Brzostowicz in view of Van Ooyen 1 and Cunningham. Thus, our comments below are based on this tripartite rejection. If our interpretation of the rejection is incorrect, the Examiner is requested to reissue the Office action with the rejection as intended.

At the outset we note that all arguments made in this paper concerning the other §103 rejections, particularly with respect to Brzostowicz, Van Ooyen 1, and Cunningham are readopted and reasserted with respect to this rejection as if fully set forth here.

Brzostowicz, Van Ooyen 1, and Cunningham are summarized above.

In making the rejection, the Examiner acknowledged that Brzostowicz "do[es] not teach the use of genus *Xanthophyllomyces (Phaffia)* as the recombinant microorganism use[d] to express the recombinant proteins." (Paper No. 20070726 at 14.)

To fill the acknowledged gap, the Examiner relied on Van Ooyen 1 for "teach[ing] transformed *Phaffia rhodozyma* capable of producing carotenoids, including zeaxanthin (co1.2, line 50) through introduction of plasmid comprising a suitable gene, 'crtZ' (col.5, line 62-63) into *Phaffia rhodozyma*." (*Id.*)

The Examiner, however, also acknowledged that Van Ooyen 1 "does not teach [the] production of β-cryptoxanthin in Phaffia." (*Id.* at 15.)

To fill this further acknowledged gap, the Examiner relied on Cunningham for "teach[ing] the production of zeaxanthin and β-cryptoxanthin by a microorganism that produces carotenoids and that was transformed with the β-carotene hydroxylase gene from A. thaliana (co1.5, lines 35-39; col. 6, lines 37-45)." (*Id.*) "Cunningham et al. also teach[es] E. herbicola β-carotene hydroxylase gene (col. 3, line 41 and col. 9, lines 11-19)." (*Id.*)

The Examiner then concluded that "[i]t would have been obvious to the person of ordinary skill in the art at the time of the invention was made to substitute a

known equivalent element for another to obtain predictable results." (*Id.*) The Examiner asserted that "it would have been obvious to substitute any equivalent β-carotene hydroxylase gene, including that of Erwinia herbicola to produce zeaxanthin and β-cryptoxanthin in Phaffia," and that "it would have been obvious to substitute *Phaffia rhodozyma* as a functionally equivalent microorganism that is useful for production of carotenoids, for any of the microorganisms taught by Brzostowicz et al." (*Id.*)

Initially, we note that claims 2-3, 6, and 9-10 have been cancelled, without prejudice. Therefore, the rejection is moot and should be withdrawn with respect to claims 2-3, 6, and 9-10.

With a view toward furthering prosecution, claim 1 has been amended to recite "[a] process for producing zeaxanthin and ß-cryptoxanthin which comprises cultivating a recombinant *Xanthophyllomyces dendrorhous* (*Phaffia rhodozyma*) ATCC96815 which expresses a ß-carotene hydroxylase gene that is originated from *Flavobacterium* sp. R1534 WT (ATCC21588) or *Erwinia herbicola* ATCC39368 in an aqueous nutrient medium under aerobic conditions, and isolating the resulting carotenoids from the cells of said recombinant microorganism or from the cultured broth, wherein the ß-carotene hydroxylase gene is expressed in the recombinant *Xanthophyllomyces dendrorhous* using an expression vector containing control sequences of glyceraldehyde-3-dehydrogenase gene."

As noted above, the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *Glaug*, 62 USPQ2d at 1152. If the PTO fails to meet its burden, then the applicant is entitled to a patent. (*Id.*) When patentability turns on the

question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR*, 127 S.Ct. at 1731-32 (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley*, 60 USPQ2d at 1008. Moreover, the factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence of record***." *Lee*, 61 USPQ2d at 1433 (emphasis added). *See also Examination Guidelines for Determining Obviousness*, 72 Fed. Reg. 57526, 57528 (October 10, 2007) ("The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.").

Respectfully, we submit that the rejection is devoid of *any* evidence - or even argument - in support of the proposed combination. All that is there is a conclusory statement that "it would have been obvious to substitute any equivalent β-carotene hydroxylase gene, including that of Erwinia herbicola to produce zeaxanthin and β-cryptoxanthin in Phaffia," and that "it would have been obvious to substitute *Phaffia rhodozyma* as a functionally equivalent microorganism that is useful for production of carotenoids, for any of the microorganisms taught by Brzostowicz et al." (Paper No. 20070726 at 15). What the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Brzostowicz in view of Van Ooyen 1 and Cunningham to arrive at the claimed method.

As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem.*, 492 F.3d at 1357 (citing *KSR*) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Levengood*, 28 USPQ2d at 1301-02. But this is precisely what the Examiner has done here.

At bottom, the Examiner has adopted a sound bite from *Ex parte Smith* – "*KSR* forecloses Appellant's argument that a specific teaching is required for a finding of obviousness" – without regard to its context or the actual Supreme Court cases from which it was adopted. In *Smith*, the technology at issue was a simple pocket insert for a book. And, the issue presented was, *inter alia*, whether it would have been obvious to glue two separate sheets to form a continuous two-ply seam. Here, however, the technology is significantly more complex than in *Smith*. Indeed, the Examiner has apparently concluded that the art is "unpredictable." (Paper No. 20070726 at 9). Unlike the Examiner's one-size-fits-all approach, the Supreme Court acknowledged that some obviousness determinations are complicated and required a multifactorial approach – involving a review of multiple patents, an evaluation of the demands in the marketplace, and the knowledge of those skilled in the art. In these circumstances, the Supreme Court reaffirmed that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 127 S.Ct. at 1731-32. Quoting with approval from *In re Kohn*, the Supreme Court reaffirmed that "there

must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.*

We respectfully submit that a careful reading of *Smith* and *KSR* requires a conclusion that the present rejection falls short of making out a *prima facie* case. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing so, we observe again that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations must be taught or suggested by the prior art***." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)) (emphasis added).

Assuming *arguendo* that Brzostowicz is properly combinable with Van Ooyen 1 and Cunningham, which it is not, such a combination does not produce amended claim 1. As acknowledged by the Examiner, Brzostowicz "do[es] not teach the use of genus *Xanthophyllomyces (Phaffia)* as the recombinant microorganism use[d] to express the recombinant proteins," and Van Ooyen "does not teach [the] production of β-cryptoxanthin in Phaffia." (Paper No. 20070726 at 14-15).

Unfortunately for the Examiner, Cunningham fails to fill these factual gaps. Cunningham discloses "the DNA sequence for ***eukaryotic genes*** encoding ε,

isopentenyl pyrophosphate isomerase (IPP) and β-carotene hydroxylase as well as vectors containing the same and hosts transformed with said vectors." Col. 1, lines 8-11. Cunningham discloses that the "method of the present invention comprises ***transforming a prokaryotic host with a DNA which may contain a eukaryotic or prokaryotic carotenoid biosynthetic gene*****.....**" Col. 6, lines 65-67. Cunningham discloses that it is an "object of this invention is to provide isolated ***eukaryotic genes*** which encode enzymes involved in carotenoid biosynthesis; in particular, ε cyclase, IPP isomerase and β-carotene hydroxylase," specifically from *A. thaliana*. Col. 2, lines 34-37; col. 3, lines 35-37; Figure 5 (SEQ ID NO: 3). ***Cunningham does not disclose the transformation of an eukaryotic host with a prokaryotic gene, as currently claimed.*** Thus, the rejection falls short factually.

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the rejections, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on February 5, 2008.

Eileen M. Ebel, Reg. No. 37,316

Respectfully submitted,

By: _____

Eileen M. Ebel
Registration No. 37,316
BRYAN CAVE LLP
1290 Avenue of the Americas
33rd Floor
New York, NY 10104-3300
Phone: (212) 541-2000
Fax: (212) 541-4630